Realities of Expectorated Sputum Collection in the Pediatric Cystic Fibrosis Clinic

Dhenuka K. Radhakrishnan, MD; Mary Corey, PhD; Sharon D. Dell, MD

Objectives: To determine the proportion of pediatric patients with cystic fibrosis who do not produce expectorated sputum during routine ambulatory clinic visits and to identify clinical predictors of these patients.

Design: Cross-sectional study.

Setting: The cystic fibrosis clinic at The Hospital for Sick Children, Toronto, Ontario.

Participants: One hundred eighty-three patients aged 6 to 18 years who attended the cystic fibrosis clinic between March 1, 2004, and November 30, 2004.

Intervention: Study patients were asked to expectorate sputum for bacterial culture.

Main Outcome Measures: The proportion of patients unable to produce expectorated sputum was determined. Age, sex, forced expiratory volume in 1 second, pancreatic sufficiency, body mass index, and antibiotic use were compared between patients producing sputum and those not producing sputum.

Results: Eighty-three patients (45%) did not expectorate sputum. Patients not producing sputum compared with those producing sputum were younger (mean age, 10.3 years vs 13.9 years, respectively; difference, 3.6 years; 95% confidence interval, 2.6-4.5) and had higher forced expiratory volume in 1 second (mean forced expiratory volumes in 1 second, 88% of predicted vs 72% of predicted, respectively; difference, 16%; 95% confidence interval, 10.1-22.2). Eighty-eight percent of patients not producing sputum had cough and 45% reported sputum production at home.

Conclusions: Almost half of pediatric patients with cystic fibrosis aged 6 years and older do not expectorate sputum in the clinic, although nearly half of these patients do report producing sputum at home. The utility of home collection on the morning of a clinic visit and/or hypertonic saline induction should be evaluated to increase the number of useful specimens for microbiological culture.

Arch Pediatr Adolesc Med. 2007;161:603-606

THE MANAGEMENT OF PATIENTS WITH Cystic Fibrosis (CF) includes the use of antimicrobial medications based on the culture results of routine expectorated sputum samples that are collected at each clinic visit. Expectorated sputum samples have been shown to closely agree with lower-airway culture results from bronchoalveolar lavage. Patients younger than 6 years are generally thought to lack the oromotor coordination to expectorate sputum on demand, so in these younger patients, nasopharyngeal suction specimens and throat swab cultures have been used as surrogate representations of lower-airway colonization. However, the validity of using nasopharyngeal suction specimens or throat swab cultures, which may overrepresent bacteria in the oronasopharynx, is controversial.

Previous studies and clinical experience reveal that many pediatric patients with CF aged 6 years and older still do not produce sputum. To our knowledge, whether the lack of sputum production in this group is related to differences in disease severity has not been previously systematically studied and reported.

The objective of this study was to identify clinical differences between pediatric patients with CF who are able to expectorate sputum in the clinic and those who are not. We hypothesized a priori that younger children with better lung function and better nutritional status would have less severe lung disease and therefore be less likely to expectorate on demand. We also hypothesized that girls would be less likely than boys to expectorate owing to gender-related social stereotypes.

METHODS

This is a cross-sectional study design that included all of the patients aged 6 to 18 years with CF attending our ambulatory clinic between March 1, 2004, and November 30, 2004. Toronto, Ontario, has a very large multiethnic clinic with a wide catchment area stretching from
Table 1. Characteristics of Study Patients vs Unscreened Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Unscreened Patients (n = 25)</th>
<th>Study Patients (n = 180)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>12.4 ± 3.1</td>
<td>12.3 ± 3.7</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>12 (48)</td>
<td>89 (49)</td>
</tr>
<tr>
<td>FEV1, mean ± SD, % of predicted</td>
<td>84 ± 21</td>
<td>79 ± 22</td>
</tr>
<tr>
<td>Pancreatic insufficient, No. (%)</td>
<td>25 (100)</td>
<td>156 (87)</td>
</tr>
</tbody>
</table>

Abbreviation: FEV1, forced expiratory volume in 1 second.
*Three patients not producing sputum were excluded from analysis, as they were unable to perform pulmonary function testing.

Table 2. Comparison of Patients Producing Sputum and Patients Not Producing Sputum

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Not Producing Sputum (n = 80)**</th>
<th>Patients Producing Sputum (n = 100)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>10.3 ± 3.7</td>
<td>13.9 ± 2.9</td>
<td>3.6 (2.6-4.5)†</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>35 (44)</td>
<td>54 (54)</td>
<td>0.66 (0.37-1.20)‡</td>
</tr>
<tr>
<td>FEV1, mean ± SD</td>
<td>88 ± 20</td>
<td>72 ± 21</td>
<td>16 (10.1-22.2)†</td>
</tr>
<tr>
<td>% of predicted</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic insufficient, No. (%)</td>
<td>64 (80)</td>
<td>92 (92)</td>
<td>0.35 (0.14-0.86)‡</td>
</tr>
<tr>
<td>BMI z score, mean ± SD</td>
<td>-0.07 ± 1.12</td>
<td>-0.45 ± 1.16</td>
<td>0.38 (0.04-0.72)‡</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FEV1, forced expiratory volume in 1 second.
**Three patients not producing sputum were excluded from analysis, as they were unable to perform pulmonary function testing.
†Values are expressed as difference (95% confidence interval).
‡Values are expressed as odds ratio (95% confidence interval).

RESULTS

Although 211 patients from the SickKids CF database were eligible for study, 25 patients did not attend their clinic appointment during the study duration and were therefore not screened for sputum production (Figure 1). This resulted in a participation rate of 88% of the population with CF. A comparison of these unscreened patients with study participants showed no significant differences in age, sex, or FEV1 (Table 1). An additional 3

central southern Ontario to northern Ontario, including urban, suburban, and rural settings. Because Canada has a universal health care system, all children who live within the catchment area are referred to our clinic after diagnosis, regardless of socioeconomic or health insurance status. According to our routine clinic practice, an attempt was made to collect expectorated sputum samples from all of the patients aged 6 to 18 years with CF (sweat chloride level >60 mmol/L or 2 CFTR gene mutations) visiting the SickKids ambulatory clinic during the study period. Children initially unable to expectorate sputum independently were coached to do so by 2 experienced CF clinic nurses (Susan Carpenter, RN, and Jennifer Leaist, BScN). The CF clinic nurses routinely macroscopically examine all sputum samples; the samples that appear mucoid and purulent are sent for culture, whereas salivalike specimens are rejected. Children who were able to expectorate a suitable (nonsalivary) sample were considered patients producing sputum, whereas those unable to expectorate were considered patients not producing sputum. Children were studied only once during the study time.

The SickKids CF clinic database and patient records were used to analyze differences in forced expiratory volume in 1 second (FEV1), age, sex, pancreatic sufficiency, body mass index (BMI), bacterial colonization, and antibiotic use between patients producing sputum and those not producing sputum. The FEV1 was measured according to published American Thoracic Society criteria and pediatric reference equations. Pancreatic sufficiency was determined in all of the patients by fecal fat collection. The BMI was calculated from the weight and height at the incident clinic (calculated as the weight in kilograms divided by the height in meters squared) and then compared with age-adjusted BMI tables for healthy children to determine the BMI z score. Standardized symptom checklists, which include among other parameters information on cough and home sputum production, were completed by the CF clinic nurses at the start of each visit from patients with CF. Cough and sputum production were classified into 1 of 4 categories: none, occasional, with physiotherapy (airway clearance techniques) only, or daily. For patients not producing sputum, symptom checklists were used to identify which patients had evidence of cough and sputum production at home during the preceding year. When symptom checklists were incomplete, a review of clinic notes from the physician and physiotherapists was used to determine the presence of cough and sputum production at home. Ethical approval for this study was obtained from the hospital’s local internal review board. In addition, all of the patients included in this study had previously provided written informed consent or assent for the confidential collection and use, for research purposes, of their disease-specific information in the SickKids CF clinic database.

Patient and disease characteristics in patients producing sputum were compared with those in patients not producing sputum using t tests and chi² analysis as appropriate. Logistic regression was used to determine independent predictors of sputum production.
patients were excluded, as they had received a double lung transplant prior to the study period.

Eighty-three patients (45% of screened clinic patients) were not able to produce sputum. Patients not producing sputum as compared with those producing sputum were significantly younger (mean ± SD age, 10.3 ± 3.7 years vs 13.9 ± 2.9 years, respectively; difference, 3.6 years; 95% confidence interval [CI], 2.6-4.5), as a group had a higher mean FEV1 (mean ± SD FEV1, 88% ± 20% vs 72% ± 21% of predicted, respectively; difference, 16%; 95% CI, 10.1-22.2), and had higher BMI (72% ± 21% of predicted, respectively; difference, 16%; 95% CI, 10.1-22.2), and had higher BMI scores (mean ± SD BMI z scores, −0.07 ± 1.12 vs −0.45 ± 1.16, respectively; difference, 0.38; 95% CI, 0.04-0.72) (Table 2). However, there were 4 patients not producing sputum who had severe lung disease (FEV1 < 30% of predicted) (Figure 2).

The ability to produce sputum did not differ between boys and girls. In fact, logistic regression showed that age (odds ratio, 0.75; 95% CI, 0.67-0.83), FEV1 (odds ratio, 1.03; 95% CI, 1.01-1.05), and pancreatic insufficiency (odds ratio, 0.32; 95% CI, 0.12-0.91) were independent predictors of sputum production, whereas sex and BMI were not (Table 3). Eighty-eight percent of patients not producing sputum were known to cough and 45% reported having sputum production at home (Figure 3).

Of the patients producing sputum, 28% were receiving macrolide antibiotics for a mean of 10.2 months, whereas only 16% of patients not producing sputum were receiving macrolides for a mean of 3.6 months; however, this difference did not reach statistical significance (Table 4). A significantly higher proportion of patients producing sputum were receiving inhaled antibiotics as compared with those not producing sputum (87% vs 58%, respectively; OR, 4.8; 95% CI, 2.3-10.1). There was no difference in the use of intravenous antibiotics between patients who produced sputum and those who did not, and they received a mean of 2.9 and 2.2 courses of intravenous antibiotics, respectively.

It is generally presumed that most children older than 6 years with CF are able to expectorate sputum for microbiological evaluation and directed antibiotic treatment. We have shown that up to 45% of these patients, in fact, do not provide sputum samples at a routine clinic visit. Younger age, pancreatic sufficiency, and higher FEV1 were found to predict patients not producing sputum, confirming our hypothesis that children with less severe disease would be less likely to produce sputum. Patients earlier in their disease state with higher lung function likely have less stasis of pulmonary secretions and are therefore unable to expectorate on demand. Furthermore, patients who produced sputum and as a group had worse lung function were more likely to be receiving inhaled antibiotics, again confirming the role of disease severity in producing sputum.

In this study, the higher rate of sputum production in girls compared with boys was not significant and reflected the lower FEV1 in girls. Logistic regression confirmed that FEV1 but not sex predicted sputum production, suggesting that gender-related social stereotypes did not contribute to variations in sputum production as we had hypothesized.

**Table 3. Adjusted Odds Ratios for Risk of Status as Not Producing Sputum**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>0.75 (0.67-0.83)</td>
</tr>
<tr>
<td>Female</td>
<td>0.78 (0.38-1.59)</td>
</tr>
<tr>
<td>FEV1, % predicted†</td>
<td>1.03 (1.01-1.05)</td>
</tr>
<tr>
<td>Pancreatic insufficient §</td>
<td>0.32 (0.12-0.91)</td>
</tr>
<tr>
<td>BMI z score‡</td>
<td>0.88 (0.60-1.29)</td>
</tr>
</tbody>
</table>

*Odds ratio is per unit (percentage predicted).
†Odds ratio is per unit (percentage predicted).
‡Odds ratio is per year of age.
§Odds ratio is per unit (normal deviate).

**Table 4. Antibiotic Use During the Previous 5 Years Among Patients Producing Sputum and Patients Not Producing Sputum**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Patients, %</th>
<th>Mean Duration, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Producing Sputum</td>
<td>Not Producing Sputum</td>
</tr>
<tr>
<td>Antistaphylococcal*</td>
<td>78.6</td>
<td>85.5</td>
</tr>
<tr>
<td>Macrolide†</td>
<td>27.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Inhaled‡</td>
<td>86.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Intravenous</td>
<td>35.7</td>
<td>27.7</td>
</tr>
</tbody>
</table>

*Antistaphylococcal therapy included cephelexin, amoxicillin, and cloxacillin sodium.
†Macrolides included azithromycin and clarithromycin.
‡Inhaled antibiotics included colimycin and tobramycin.
Early intervention with antibiotic therapy directed against organisms cultured from the lower airways has become the standard of care in patients with CF. At our institution, patients who are unable to expectorate sputum have throat swab cultures taken as a surrogate representation of lower-airway flora. For patients with progressive lung disease, throat swab cultures are likely insufficiently sensitive to detect all of the colonizing lung pathogens; however, frequent bronchoalveolar lavage cultures would be too invasive and impractical for routine assessment. If early antibiotic intervention is really important, it is imperative to identify additional noninvasive methods to obtain lower-respiratory samples.

Although we found that younger age and less severe lung disease predicted the patients not producing sputum, we did identify a portion of our clinic population who did not expectorate sputum on demand despite severe lung disease. While bronchoalveolar lavage is certainly an option for obtaining lower-airway culture in these patients, it is also important to identify alternative, reliable, noninvasive methods to obtain lower-airway cultures routinely at each clinic visit.

Nearly half of the patients who failed to expectorate in the clinic did report producing sputum at home, suggesting that home sputum collection on the morning of a clinic visit may be an option to improve culture yield. Sputum collection after chest physiotherapy or hypertonic saline inhalation may be additional noninvasive methods to increase lower-airway culture yield.

One of the main strengths of this study is that it is a population-based study generalizable to the North American pediatric CF population. During the 9-month study period, we were able to recruit 88% of patients followed up in our clinic, and those who were missed did not differ significantly in terms of age, sex, or markers of disease severity. We therefore believe that most other pediatric CF clinics are experiencing the same difficulty in obtaining expectorated sputum samples. A limitation of our study is that we did not explore the effect of asthma or albuterol use on sputum production, and these may have been contributing factors distinguishing patients who produced sputum from those who did not.

Interestingly, expectorated sputum culture results, including microbiological cultures and inflammatory markers, are often used as outcome measures in CF clinical studies. The ability of children to produce expectorated sputum needs to be considered in the feasibility of clinical trial designs. This study provides useful information for sample size calculations and sampling limitations in future pediatric clinical studies using expectorated sputum as an outcome measure.

Almost half of children and adolescents with CF do not expectorate sputum in the ambulatory clinic setting. Younger patients with better lung function are less likely to expectorate sputum, but a significant number of children with advanced lung disease are also unable to expectorate. Additional noninvasive methods are required to optimize microbiological lower-airway sampling in these patients if early antimicrobial therapy of lower-airway pathogens is important.

REFERENCES


CONCLUSIONS